CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

BIFENAZATE

Chemical Code # 5657, Tolerance # 52750

Original Date: 3/30/00
Revised: 8/25/00

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap; no adverse effect
Teratology, rabbit:	No data gap; no adverse effect
Gene mutation:	No data gap; no adverse effect
Chromosome effects:	No data gap; no adverse effect
DNA damage:	No data gap; no adverse effect
Neurotoxicity:	No study on file, one not required at this time.

Toxicology one-liners are attached.

All record numbers through 174371 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T000825
Moore, 8/25/00

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 113; 174365; "104-Week Combined Chronic Dietary Toxicity and Oncogenicity Study in Rats with D2341"; (J.L. Ivett; Covance Laboratories Inc., Vienna, VA; Study ID. Covance 798-229; 3/19/99); Sixty Sprague-Dawley rats/sex/group received 0, 20, 80 or 160 (females only) or 200 ppm (males only) of D2341 Technical (lot no. PP159945, purity: 92.5%) in the diet for 104 weeks ((M): 0, 1.0, 3.9 or 9.7 mg/kg/day, (F): 0, 1.2, 4.8, or 9.7 mg/kg/day). Mean body weights for the high dose animals were less than those of the controls for the first year with the greatest difference after 13 weeks of treatment ($p<0.05$, (M) 95.2% of control, (F) 90.6% of control). There were no treatment-related effects upon survivability. By the end of the study, the mean body weights were not significantly affected by the treatment. Mean food consumption was only minimally affected by the treatment during the first 6 months of the study. Hematologically, the mean rbc counts and hemoglobin and hematocrit values for the 160 ppm females were lower than those of the controls during the first year of the study ($p<0.05$). Extramedullary hematopoiesis was minimally increased in the adrenal cortex, liver, and spleen of the high dose females over that of the controls. Likewise, there was increased pigment in the sinusoidal cells of the liver and in the spleen of these animals. For the males in the 200 ppm group, the mean cholesterol level was lower than that of the control throughout the study ($p<0.05$ through week 78) and an increased incidence of chronic inflammation of the pancreas and an increased incidence and severity of spongiosis hepatis in the liver were noted. However, the clinical results did not reveal any concomitant effects related to the functioning of the pancreas or liver. **No adverse effect indicated.** The maximally tolerated dose was not attained. However, the selected doses were credibly derived from the results of the 90-day subchronic study. By all considerations, the animals appeared to adapt to the presence of the test material in their diet over the time course of the study. **No oncogenicity apparent. Chronic NOEL: (M/F)** 80 ppm ((M): 3.9 mg/kg/day, (F): 4.8 mg/kg/day) (based upon lower mean body weights for the 200 ppm males and the 160 ppm females, the hematological effects noted for the 160 ppm females); **Study acceptable**. (Moore, 7/14/00)

CHRONIC TOXICITY, RAT

See Combined, Rat

CHRONIC TOXICITY, DOG

** 110; 174337; "One Year Dietary Toxicity Study in Dogs"; (E.I. Goldenthal; MPI Research, Mattawan, MI; Study ID. 399-192; 1/20/99); Five beagle dogs/sex/group received 0, 40, 400 or 1000 ppm of D2341 Technical (lot no. PP159981B, purity: 92.4%) in the diet for 1 year (M: 0, 1.01, 8.95, 23.9 mg/kg/day, F: 0, 1.05, 10.4, 29.2 mg/kg/day). There were no treatment-related effects noted for clinical signs or mean body weight. Red blood cell counts were reduced throughout the study in conjunction with lower mean hemoglobin and hematocrit for the 1000 ppm treatment group ($p<0.05$ or $p<0.01$). Mean corpuscular volume was increased for the 400 ppm treatment group ($p<0.05$ or $p<0.01$), more than even the 1000 ppm group. Mean platelet count was greater for the 400 and 1000 ppm groups ($p<0.05$ or $p<0.01$). Likewise, the mean number of reticulocytes in relation to the number of red blood cells was increased in a dose-related manner for the two higher treatment groups ($p<0.05$ or $p<0.01$). Mean total serum bilirubin was increased for both of these groups ($p<0.05$ or $p<0.01$). Histologically, these effects on the red blood cells and platelets were confirmed by the increased incidence and severity of myeloid hyperplasia noted in the bone marrow of the 400 and 1000 ppm treatment groups. In addition, trace levels of pigment were noted in the kidneys and liver of these animals. **No adverse effect indicated. NOEL:** (M/F): 40 ppm (M: 1.01 mg/kg/day, F: 1.05 mg/kg/day) (based upon myeloid hyperplasia and a dose-related decrease in numbers of erythrocytes and increased numbers of platelets and level of serum bilirubin in the 400 and 1000 ppm treatment groups). **Study acceptable.** (Moore, 6/27/00)

ONCOGENICITY, RAT

See Combined, Rat

ONCOGENICITY, MOUSE

** 111; 174335; "78-Week Dietary Oncogenicity Study in Mice with D2341"; (J.L. Ivett; Covance Laboratories Inc., Vienna, VA; Study No. 798-230; 3/18/99); Fifty CD-1 mice/sex/group were treated in the diet with 0, 10, 100 or 175 (females) or 225 ppm (males) of D2341 Technical (lot no. PP159945, purity: 92.5%) for 18 months (M: 0, 1.5, 15.4, 35.1 mg/kg/day, F: 0, 1.9, 19.7, 35.7 mg/kg/day). There was no treatment-related effect on survival or clinical signs. Mean body weights for the high dose males were less than those of the controls up through 26 weeks ($p<0.05$, week 26: 93.6% of control). The mean body weights for the high dose females were less than those of the controls throughout the study ($p<0.05$, week 79: 93.1% of control). Food consumption was not affected by the treatment. The mean white blood cell and lymphocyte counts for the 100 and 225 ppm males were less than those of the controls at 52 weeks ($p<0.05$). The mean kidney weights were less than those of the controls for the 100 and 225 ppm males and the 175 ppm females ($p<0.05$). The mean liver weight for the high dose males was greater than that of the controls ($p<0.05$). The mean relative kidney weights for the 100 and 225 ppm males, as well, were less than those of the controls ($p<0.05$). The mean relative liver weights for the high dose males and females were greater than those of the controls ($p<0.05$). Microscopic examination revealed an increased incidence of extramedullary hematopoiesis in the liver of the high dose females. However, there was not a well defined dose-response. Similarly, there was an increased incidence of hepatocellular adenoma for the high dose males above that of the control (10/48 versus 5/49, $p=0.12$). However, this response was not accompanied by an increased incidence or severity in hepatocellular hyperplasia and the presence of altered foci and was considered to incidental to the treatment. **No adverse effect indicated. Chronic NOEL: (M)** 10 ppm (1.5 mg/kg/day) (based upon lower mean white cell and lymphocyte counts and lower mean kidney weights for the 100 ppm males), **(F)** 100 ppm (19.7 mg/kg/day) (based upon lower mean body weights and kidney weights for the 175 ppm females); **Oncogenicity not evident. Study acceptable.** (Moore, 6/29/00)

REPRODUCTION, RAT

** 112; 174338; "A Two-Generation Reproductive Toxicity Study of D2341 in Rats"; (J.L. Schardein; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-155039; 3/10/99); Thirty rats/sex/group were dosed in the diet with 0, 20, 80, or 200 ppm of D2341 Technical (lot no. PP15 9981-B, purity: 92.5%) for two generations. The treatment periods for the F0 generation included at least 10 weeks prior to mating, mating and 3 weeks each of gestation and lactation. At that time, 30 F1 weanlings/sex/group were selected as parents and treated for at least 10 weeks prior to mating, mating, and 3 weeks each of gestation and lactation. The mean body weights of the 200 ppm treatment group were lower for both generations and both sexes ($p<0.01$). In addition, the mean body weights of the 20 and 80 ppm F1 females and the 80 ppm F1 males were lower than those of the control group ($p<0.05$ or $p<0.01$). There were no treatment-related clinical signs nor effect upon food consumption. The mean liver weights for the F1 males in the 80 and 200 ppm groups and the F1 females in the 200 ppm group were lower than that of the controls ($p<0.01$). Although the relative weights of some of the organs of the females in the 200 ppm group of both generations were greater than those of the control ($p<0.05$ or $p<0.010$), the effect was related more to the lower mean body weights for that group than for any apparent effect on a particular organ. There were no treatment-related lesions in the microscopic examination. The reproductive parameters were not affected by the treatment. The only developmental effects noted were a slightly delayed balanopreputial separation for the males of the 80 and 200 ppm groups and vaginal perforation for the females of the 200 ppm group. **No adverse effect indicated. Parental NOEL:** < 20 ppm (based upon the lower mean body weights for the 20 ppm F1 females) (<F0 (M) 1.5 mg/kg/day, F1 (M) 1.7 mg/kg/day, F0 (F) 1.4 to 3.1 mg/kg/day, F1 (F) 1.4 to 3.2 mg/kg/day), **Reproductive NOEL:** 200 ppm (no effects noted at the highest dose tested) (F0 (M) 15.3 mg/kg/day, F1(M) 17.4 mg/kg/day, (F0 (F) 15.6 to 32.8 mg/kg/day, F1 (F) 15.0 to 33.6 mg/kg/day), **Developmental NOEL:** 20 ppm (based upon the delayed balanopreputial separation noted for the 80 ppm males) (F0 (M) 1.5 mg/kg/day, F1 (M) 1.7 mg/kg/day, F0 (F) 1.4 to 3.1 mg/kg/day, F1 (F) 1.4 to 3.2 mg/kg/day). **Study acceptable. (**Moore, 7/7/00)

112; 174338; "A Two-Generation Reproductive Toxicity Study of D2341 in Rats (Supplement to WIL-155039)"; (J.L. Schardein; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-155040; 3/10/99); Thirty rats/sex/group were dosed in the diet with 0, 7.5, 15, or 20 ppm of D2341 Technical (lot no. PP15 9981-B, purity: 92.5%) for two generations. The treatment periods for the F0 generation included at least 10 weeks prior to mating, mating and 3 weeks each of gestation and lactation. At that time, 30 F1 weanlings/sex/group were selected as parents and treated for at least 10 weeks prior to mating, mating, and 3 weeks each of gestation and lactation. In the F0 generation, one male in 7.5 ppm treatment group died during week 13 and one female in 15 ppm group died during week 18. In the F1 generation, one male in the 7.5 ppm group died during week 36, one male in the 20 ppm group was euthanized during week 18, one female in control died during week 17 and in the 20 ppm, one female died and one female was euthanized during week 18. None of the mortalities were treatment-related. There were no treatment-related clinical signs nor effect upon food consumption. The reproductive parameters were not affected by the treatment. There were no treatment-related effects upon the development of the pups. **No adverse effect indicated. Parental NOEL:** 20 ppm ((no effects noted at the highest dose tested) (F0 (M) 1.5 mg/kg/day, F1 (M) 1.7 mg/kg/day, F0 (F) 1.4 to 3.1 mg/kg/day, F1 (F) 1.4 to 3.2 mg/kg/day), **Reproductive NOEL:** 20 ppm (no effects at highest dose tested) (F0 (M) 1.5 mg/kg/day, F1 (M) 1.7 mg/kg/day, F0 (F) 1.4 to 3.1 mg/kg/day, F1 (F) 1.4 to 3.2 mg/kg/day), **Developmental NOEL:** 20 ppm (no effects at the highest dosed tested) (F0 (M) 1.5 mg/kg/day, F1 (M) 1.7 mg/kg/day, F0 (F) 1.4 to 3.1 mg/kg/day, F1 (F) 1.4 to 3.2 mg/kg/day), **Study supplemental** (dose-response not established in the study) **(**Moore, 7/11/00)

TERATOLOGY, RAT

** 062; 169399; "A Developmental Toxicity Study of D2341 in Rats"; (J.L. Schardein; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-155036; 6/5/97); Twenty five mated female Sprague-Dawley rats/sex were dosed orally by gavage with 0, 10, 100 or 500 mg/kg/day of D2341 (lot no. PP159981-B) (purity: 92.5%) from day 6 through day 15 of gestation. The mean food consumption during the entire dosing period and mean body weight gain during the first 3 days of dosing of the 100 and 500 mg/kg/day treatment groups were lower than those values for the control group ($p<0.01$). There were no apparent treatment-related effects upon the development of the fetuses. Although the % postimplantation loss was significantly increased for the 100 and 500 mg/kg/day treatment groups, the response was not dose-related and the % loss/litter in the 100 and 500 mg/kg/day group was within the range of the historical control values (2.2 to 13.5%). **No adverse effect indicated**. Maternal NOEL: 10 mg/kg/day (based upon the reduced food consumption and reduced body weight gain noted for the 100 and 500 mg/kg/day treatment groups) Developmental NOEL: 500 mg/kg/day (HTD); Study **acceptable**. (Moore, 1/5/00)

TERATOLOGY, RABBIT

** 061; 169398; "A Developmental Toxicity Study of D2341 in Rabbits"; (J.L. Schardein; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-155037; 6/5/97); Twenty artificially inseminated female New Zealand White rabbits were dosed orally by gavage with D2341 (lot no. PP159981) (purity: 92.5%) from day 7 through day 19 of gestation at 0, 10, 50 or 200 mg/kg/day. One female each aborted in the control, 50 and 200 mg/kg/day groups on days 21, 20 and 26, respectively. Two females in the high dose group suffered total resorption of their offspring. All of these resorptions occurred early in gestation. There was no treatment-related effect on body weight gain or food consumption. There was no apparent treatment-related effect upon the development of the fetuses. **No adverse effects indicated**. Maternal NOEL: 200 mg/kg/day (HTD), Developmental NOEL: 200 mg/kg/day (HTD); Study **acceptable**. (Moore, 1/4/00)

061; 169398; "Range-finding Developmental Toxicity Study in New Zealand White Rabbits"; (K.H. Denny; MPI Research, Mattawan, MI; Study ID.: 399-182; 5/7/96); Five artificially inseminated females/group were dosed orally by gavage with 0, 125, 250, 500, 750 or 1000 mg/kg/day of D-2341 (purity: 90.1%) from day 7 through day 20 of gestation. One control female died on gestation day 6. Three of the 250 mg/kg females aborted on days 10, 13 and 13. One 500 mg/kg female was euthanized

in extremis on day 14 and two other animals aborted on days 12 and 14, respectively. One 750 mg/kg animal was found dead on day 10 and the other 4 females aborted on days 13, 14, 14, and 15. Two 1000 mg/kg females died on days 4 and 14 and one animal aborted on day 14. Body weight gain was affected in a dose-related manner at 500 mg/kg/day and greater. Maternal NOEL: 125 mg/kg/day (based upon the increased number of abortions in the 250 mg/kg group), Developmental NOEL: can not be established due to the low number of females carrying to term in the higher dose groups. **Supplemental Study**. (Moore, 1/3/00)

GENE MUTATION

** 063; 169400; "Bacterial Reverse Mutation Assay with an Independent Repeat Assay (Ames Assay)"; (V.O. Wagner and N. Coffman; Microbiological Associates, Inc., Rockville, MD; Study No. G96AJ85.502001; 7/9/96); S. typhimurium strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2 uvrA were treated using the plate incorporation method for 48 to 72 hours at 37° C with D2341 (lot no. PP159945, purity: 90.2%) at concentrations ranging from 10 to 5000 µg/plate under conditions of +/- activation. Two trials were performed. Each treatment level was plated in triplicate. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated**. Study **acceptable**. (Moore, 1/13/00)

** 065; 169402; "In Vitro Mammalian Cell Gene Mutation Test with an Independent Repeat Assay (Mouse Lymphoma Mutagenesis Assay)"; (R.H.C. San and J.J. Clarke; Microbiological Associates, Inc., Rockville, MD; Study No. G96AJ85.702001; 9/30/96); Mouse lymphoma L5178Y cells (clone 3.7.2C ($TK^{+/-}$)) were treated with D2341 (lot no. PP159945, purity: 90.2%) at concentrations ranging from 5 to 50 µg/ml (nonactivation) and 25 to 1000 µg/ml (activation) for 4 hours at 37° C. Two independent trials were performed with duplicate cultures/treatment level and 3 replicates per culture. An Aroclor 1254-induced rat liver S9 fraction was used to activate the test material. Cell viability and mutation frequency were determined and compared to the solvent control level. Mutant colonies were sized over a range of 0.2 to 1.1 mm for the solvent and positive control samples. The mutant frequency of the solvent control for both of the activated assays was much higher than frequencies of the treated samples. Although these results call into question the validity of the solvent control values, the study results for the treated samples did not indicate any increase in the mutation frequency. **No adverse effect indicated**. Study **acceptable**. (Moore, 1/11/00)

CHROMOSOME EFFECTS

** 066; 169403; "In Vitro Mammalian Cytogenetic Test with an Independent Repeat Assay"; (R. Gudi and E.H. Schadly; Microbiological Associates, Inc., Rockville, MD; Study No. G96AJ85.335; 12/3/96); Chinese Hamster Ovary cells ($CHO\text{-}K_1$) (CCL 61) were incubated with D2341 (lot no. PP159945; purity: 90.2%) at concentrations ranging from 12 to 375 µg/ml (nonactivated, Trial #1), 20 to 1250 µg/ml (activated, Trial #1), 12 to 94 µg/ml (nonactivated, Trial #2) or 20 to 236 µg/ml (activated, Trial #2) at 37° C. In Trial #1, both nonactivated and activated samples received 6 hours of treatment and an additional 14 hours of incubation. In Trial #2, nonactivated samples received 20 or 44 hours of treatment. The activated samples received 6 hours of treatment followed by 14 or 38 hours of incubation. In both assays, the cells were incubated the last 2 hours with Colcemid prior to fixation. All of the incubations were performed with duplicate cultures. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the percentage of cells with chromosomal aberrations. **No adverse effect indicated**. Study **acceptable**. (Moore, 1/13/00)

DNA DAMAGE

** 064; 169401; "Micronucleus Cytogenetic Assay in Mice"; (R. Gudi; Microbiological Associates, Inc., Rockville, MD; Study No. G96AJ85.122; 10/4/96); Five male mice/group/time point were dosed intraperitoneally (ip) with 0, 96, 192, or 384 mg/kg of D2341 (lot no. PP159945) (purity: 90.2%). Likewise, five female mice/group/time point were dosed ip with 0, 50, 100 or 200 mg/kg. An additional five males and five females each were dosed at 384 and 200 mg/kg, respectively. For the positive

control, five mice/sex were dosed with 60 mg/kg of cyclophosphamide. Treated animals were euthanized at 24, 48 and 72 hours after dosing. The animals treated with the positive control were euthanized 24 hours after dosing. Femoral bone marrow was harvested and evaluated for the presence of micronuclei in polychromatic erythrocytes (PCE). One thousand polychromatic erythrocytes were evaluated per animal. Three of the males in the 384 mg/kg treatment group died. Treatment-related signs included lethargy. Treatment with the test material did not result in an increase in the number of micronuclei per 1000 PCE's. **No adverse effect indicated**. Study **acceptable**. (Moore, 1/6/00)

NEUROTOXICITY

No study submitted

SUBCHRONIC STUDIES

059; 169396; "90-Day Dietary Toxicity Study in Rats with D2341" (J. A. Trutter, Covance Laboratories Inc., Vienna, VA., Covance Study No.: 798-227, 06/06/97). D2341 Technical Grade (Lot # DS042895; 91 % purity) was administered to 4 groups of Crl:CD®BR rats (10/sex/group) ad libitum in the diet for at least 90 days at dosage levels of 0, 40, 200, and 400 ppm. All animals survived the study. No compound-related clinical signs, ophthalmoscopic observations, serum chemistry changes, or urinalysis findings were observed in any of the test groups. Neurobehavioral testing showed no evidence of any compound-related effects. At necropsy, none of the macroscopic tissue changes were attributable to administration of the test material. The dietary administration of D2341 resulted in dose-related effects on body weight (7 to 16% reduction), food consumption (8 to12% reduction), clinical hematology (i.e., reduced erythrocyte count, hemoglobin, and hematocrit values), and histopathological changes (i.e., liver, spleen and adrenal cortex) in the 200 and 400 ppm groups compared to the controls. **No adverse effects**. NOEL (M/F): 40 ppm; (M): 2.7 mg/kg/day; (F): 3.2 mg/kg/day, based on changes in body weight, food consumption and clinical hematology at 200 and 400 ppm ($p \leq 0.05$) and also histopathological changes at $\geq$ 200 ppm. **Acceptable**. (Eya, 01/31/99).

060; 169397; "90-Day Dietary Toxicity Study in Dogs, Test Article: D2341" (E.I. Goldenthal, MPI Research, Mattawan, MI, Laboratory Study Identification No.: 399-191, 08/20/97). D2341 Technical Grade (Lot # PP159981B; 92.4 % purity) was administered to 3 groups of beagle dogs (4/sex/group) in the diet for 92-93 days at dosage levels of 0, 40, 400, and 1000 ppm. All dogs survived to study termination. No test material related clinical signs, macroscopic pathological changes, or significant finding in the ophthalomological and physical examination were observed. Body weight gain for dogs at 1000 ppm was slightly decreased, and the food consumption was lower in (F): 400 and 1000 ppm compared to controls. The most significant hematological findings were decreased erythrocytes, hemoglobin and hematocrit at 400 and 1000 ppm. A compensatory increase in reticulocyte counts, mean corpuscular volume, incidence of anisocytosis , and platelet counts occurred as well. Cholesterol, alkaline phosphatase, and bilirubin values were increased in males at 1000 ppm. Absolute and relative liver weights were increased at 400 and 1000 ppm. Microscopically, the test material related hepatocellular hypertrophy was seen in (F): 400 ppm, and (M/F): 1000 ppm. Also, a test material related brown pigment was present in Kupffer cells at 400 and 1000 ppm dogs. **No adverse effects**. NOEL (M/F): 40 ppm (M: 0.9 mg/kg/day; F: 1.3 mg/kg/day) based on the hepatocellular hypertropy, changes in Kupffer cells, and reduction of erythrocytes, hemoglobin and hematocrit at 400 and 1000 ppm. **Acceptable**. (Eya, 02/07/00).

058; 169395; "21-Day Dermal Toxicity Study in Rats, Test Article: D2341" (E. I. Goldenthal, MPI Research, Mattawan, MI., Laboratory Identification No.: 399-197, 10/20/98). D2341 (Lot # PP159981B; 92.5 % purity) was administered by dermal application 6 hours/day for 21-22 days to 3 groups of Sprague Dawley [Crl:CD® (BR)] VAX/Plus rats (10/sex/group) at dosage levels of 80, 400, and 1000 mg/kg/day. All rats survived to study termination. No changes were observed in the clinical signs, clinical values, ophthalmological examinations, and macroscopic pathology. Very slight dermal irritation, which was not considered toxicologically significant, was observed in the treated animals. Body weight reductions were observed in (M/F):1000 mg/kg/day and in (F):400 mg/kg/day. Food consumption was reduced at 400 and 1000 mg/kg/day. Reduction in erythrocyte counts, hemoglobin, and hematocrit were observed in (F):1000 mg/kg/day, and lower hemoglobin values were observed in (M):1000

mg/kg/day. Total bilirubin was slightly increase at 1000 mg/kg/day in females. A mild increase in urinary ketones, protein, and specific gravity, and a decrease in the urine volume were seen at 400 and 1000 mg/kg/day. Absolute and/or relative spleen weights were increased at 1000 mg/kg/day. Microscopic increases of extramedullary hematopoiesis of the spleen were seen at 400 and 1000 mg/kg/day. Systemic NOEL (M/F) = 80 mg/kg/day, based on extramedullary hematopoiesis of the spleen and body weight reduction in both sexes (technical grade material). Dermal NOEL (M/F) = 1000 mg/kg/day (no effect at highest dose tested). **Acceptable**. (Eya, 01/24/00).

METABOLISM

** 114; 174371; "Metabolism of [^{14}C] D2341 in Rats"; (R.H. McClanahan; Department of Environmental and Metabolic Fate, Department of Toxicology and Animal Metabolism, Ricera, Inc., Painesville, OH; Study No. 6455-95-0089-EF-001; 3/26/98); Sprague-Dawley Crl:CD/BR rats of both sexes were dosed with either 10 or 1000 mg/kg of [^{14}C] D2341 (lot no. CSL-94-516-73-20, radiochemical purity: $\geq$ 98%, specific activity: 34.4 mCi/mmol, label on the aromatic ring, D2341 (unlabeled), lot no. AC-1398, purity: 99.6%) by oral gavage. In the Distribution, Metabolism and Excretion study, 5 animals/sex/group were dosed and urine and feces were collected for 7 days. In the Biliary study, 3 animals/sex/group with cannulated bile ducts were dosed and urine, feces and bile were collected for 72 hours. The Pilot Pharmacokinetic and Pharmacokinetic studies were performed in which 3 animals/sex/group and 5 animals/sex/group, respectively, were dosed. In the pilot study, urine and feces for collected for 4 days and blood samples were collected via a jugular cannula for 72 hours. In the main study, urine and blood were collected for 4 days from the animals in the 10 mg/kg treatment group. In the 1000 mg/kg group, urine, feces and blood were collected for 7 days. In the Tissue Distribution study, 9 animals/sex/group were dosed. In the 10 mg/kg group, 3 animals/sex/time point were serially euthanized at 6, 24 and 48 hours after dosing. In the 1000 mg/kg group, 3 animals/sex/time point were euthanized at 18, 42 and 72 hours post-dose. Urine and feces were collected at designated intervals. Tissue samples from Distribution, Metabolism and Excretion study and the Tissue Distribution study were processed for the presence of radiolabel. Radiolabeled materials were isolated from the urine and feces derived from the Distribution, Metabolism and Excretion and the Biliary studies and structurally analyzed for a metabolic profile. The predominant route of excretion for both doses was via the feces. For the 10 mg/kg group, 66% of the administered dose (AD) was recovered in the feces with 75 to 82% of that total excreted in the first 24 hours. Radiolabel recovered in the urine and cage wash constituted 27 to 29% of the AD after 7 days. For the 1000 mg/kg treatment group, the percentage of AD recovered in the feces up to 7 days post-dose was 82% with 46 to 57% of that total recovered in the first 24 hours. The percentage of AD isolated in the urine and cage wash was 10 to 15%. The Biliary study demonstrated that the bile was a significant pathway for excretion by the 10 mg/kg treatment group with 69 to 74% of the administered dose recovered in the bile up to 72 hours after dosing. In contrast, for the high dose group, 21 to 26% of the dose was isolated in the bile by 72 hours. Recovery in the feces of the 10 mg/kg group was limited to 7 to 8% of the AD as compared to 56 to 64% of the AD for the 1000 mg/kg group. A significant fraction of the AD for the high dose group was not being absorbed. The following pharmacokinetic parameters were derived: tmax, 5 and 6 hours and 18 to 24 hours for males and females of the 10 mg/kg and 1000 mg/kg groups, respectively, Cmax, 6.4 and 5.6 µg equiv./g and 119 and 71 µg equiv./g for the males and females in the 10 mg/kg and 1000 mg/kg groups, respectively, and t1/2, 11.5 and 13.3 hours and 12 and 15.6 hours for males and females in the low and high dose groups, respectively. In the Tissue Distribution study, among the 10 mg/kg animals, maximal residue levels were noted at 6 hours with none of the radiolabel being sequestered in any of the tissues. In the 1000 mg/kg group, maximal residue levels were noted in a majority of the tissues at 18 hours post-dose for the males and 42 hours post-dose for the females. For some of the organs, appreciable levels of radiolabel were still evident at 7 days (e.g., spleen, red blood cell, liver, and kidney). Analysis of the radiolabeled moieties recovered in the feces revealed a number of modifications of the parent compound. Hydrazine oxidation, demethylation, ring hydroxylation, separation into biphenyl and hydrazinecarboxylic acid moieties and conjugation with glucuronic acid or sulfate. For the 10 mg/kg group, identified moieties extracted from the feces constituted 39% of the AD. The predominant compounds were D2341 glucuronide (6.3 to 8.9% of AD), D2341 (4.8 to 7.2% of AD) and A1530 (biphenyl, 4-hydroxy) (5.5 to 7.1% of AD). In

contrast, for the 1000 mg/kg group, the parent compound which was recovered in the feces constituted 48 to 61% of the AD. D2341 glucuronide constituted 4.7 to 5.6% of the AD. The primary moieties recovered in the urine were conjugates of D9560 (p, p'-biphenol) or sulfates of D9560 and A1530. The total of these compounds constituted 19 to 21% of the administered dose for the 10 mg/kg group and 6 to 7% of the administered dose for the 1000 mg/kg group. Major metabolites identified in the bile were A1530 (17 to 20% of AD in the 10 mg/kg group and 2.1 to 2.5% of the AD in the 1000 mg/kg group), D9477 (biphenyl, 4-hydroxy, 4'-methoxy) (17 to 19% of the AD in the 10 mg/kg and 2.8% of the AD in the 1000 mg/kg group) and D2341 glucuronide (9 to 12% of the AD in the 10 mg/kg and 9 to 13% of the AD in the 1000 mg/kg group). Overall, the test material was well absorbed at the low dose, metabolized and conjugated before being excreted in the bile. At the high dose level, a much lower percentage of the dose was absorbed. **Study acceptable.** (Moore, 7/25/00)

067; 169404; "Pilot Study of the Routes of Elimination of Radiolabel Following Oral Administration of ^{14}C-D2341 to Sprague-Dawley Rats"; (J.C. Andre and R.H. McClanahan; Department of Toxicology and Animal Metabolism, Ricerca, Inc., Painesville, OH; Project ID No. 95-0045; 2/21/97); Two animals/sex/group were dosed by oral gavage with 10 or 1000 mg/kg of [^{14}C] D2341 (specific activity: 34.4 mCi/mmol, radiochemical purity>98%, chemical purity>98%, chemical purity of nonradiolabel: 99.6%). Expired air, urine and feces were collected for 7 days. The data are useful in providing an initial assessment of the disposition of the test material in the rat. The administered radiolabel was largely recovered within 7 days. The recovery was more rapid in the lower dose group with greater than 85% of the dose accounted for within 48 hour post-dose, largely in the feces. The recovery was more prolonged in the 1000 mg/kg with the greater part of the dose accounted for between 3 and 7 days post-dose and almost entirely in the feces. There was no apparent sex-related difference in the study results. The low level of radiolabel trapped in the expired air was a function of the label being positioned on the aromatic ring and being minimally metabolized. The data were insufficient to elucidate the percentage of the administered dose which may have been absorbed. Timed blood sampling and bile duct cannulation are required in order to determine the extent to which the test material was absorbed from the gastrointestinal tract and excreted via the bile into the feces. **Supplemental** study. (Moore, 1/14/00)